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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,260	10/02/2003	Hyung-seok Kang	912-41	3476

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,260	KANG ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 12-2-08 is acknowledged.

Claims included in the prosecution are 19-35.

Claim Objections

1. Claims 19-35 are objected to because of the following informalities: the term, 'liposomes' is misspelled in several places. Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 19-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear as to what applicant intends to convey by "to a salt having surface activity' in (a) of claim 19. Furthermore, the pH of the terpenoid in this step is unclear; this is essential since in step (b), the pH is 5-8. It is basic knowledge that pH which is less than 7 is acidic and above 7 is basic. A pH of 8 is considered basic and one would expect the acid terpenoid to be in an unprotonated state at this pH and therefore, the salt is not totally converted into the acid form.

It is unclear as to what applicant intends to convey by toilet water, nutrition toilet water, cleansing water, nutrition cream, massage cream, eye cream, essence, body essence in claim 34. What is the difference between toilet water, nutrition toilet water

and cleansing water? Similar is the case with nutrition cream and massage cream; essence and body essence.

4. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 34 recites the broad recitation toilet water, essence, cleansing cream, and the claim also recites nutrition toilet water, eye essence, body essence, cleansing water which are the narrower statements of the range/limitation.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 29, 31-35 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/17523 of record.

WO teaches liposomal skin compositions containing triterpenoids, ursolic acid (page 1, lines 20-31). The method of preparation involves dissolving ursolic acid, phosphatidylcholine in ethanol and then adding this mixture to water (page 11, line 1-8, 15-19; page 16, lines 15-18; Example 1). The amounts given in millimolar quantities appear to fall within the range claimed. Product by process claims are still considered as product claims and the burden is upon applicant to show that the product claimed is different from the prior art product.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 19-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Touitou (5,716,638) by itself or in combination with Cauwenbergh (5,476,853), Hauser (4,619,794) by themselves or in combination.

Touitou discloses a method of preparation of liposomes containing lipophilic active agents, which includes terpenes. The method involves adding the lipophilic drug and Phospholipon in ethanol-propylene glycol either at room temperature or at 60 to 70 degrees, adding to distilled water and TEA (triethanolamine) and cooling the mixture

(abstract; col. 1, lines 8-32; col. 1, line 66 through col. 3, line 10; col. 4, lines 14-50; columns 5 and 6 and claims). Instant method differs from Touitou in the following way. In instant method the terpenoid is dispersed in polyol (propylene glycol) at 60-70 degrees to which TEA is added and then phospholipid solution in ethanol is added. To this mixture, water is then added. In Touitou, the lipophilic drug, phospholipid are added together in ethanol-propylene glycol mixture to which the TEA and water is added. Since the function of the base is to elevate the pH of a dispersion to alkaline values and since the addition of water to the phospholipid in the organic solvent in both Touitou and instant method, it would have been obvious to one of ordinary skill in the art at the time the invention was made to vary the steps in the method of Touitou and still expect the formation of the liposomes. Touitou also differs from instant method in the last step; that is, the addition of the acid to change the alkaline pH of the liposomal suspension. However, since the preparations of Touitou are meant for the topical application of skin, it would have been obvious to one of ordinary skill in the art to change the alkaline pH resulting from the addition of TEA in Touitou to neutral or near neutral pH by the addition of an acid since these pH levels are compatible with skin. One of ordinary skill in the art would be motivated to change the alkaline pH of Touitou to pH of 5 to 7.5 since the reference of Cauwenbergh while disclosing liposomal skin formulations such as toilet waters and skin milk teaches that the final pH of 5 to 7.5 is preferable and this pH can be obtained by the addition of either a base or an acid or buffer such as citric acid or phosphoric acid or acetate buffer (abstract; col. 3, lines 37-65; Examples 4 and 5). Although Touitou does not teach specifically triterpenoids and claimed triterpenoids,

since he teaches generic 'terpenes', it would have been obvious to one of ordinary skill in the art to use any terpene including claimed triterpenes since these are also lipophilic with a reasonable expectation of success.

Hauser discloses methods of preparation of liposomes containing encapsulated drugs. One of the methods of preparation involves hydration at an alkaline pH of about 12 and followed by lowering the pH to 7-8 (Example 2).

One of ordinary skill in the art would be motivated to use a higher pH first and then lower the pH with a reasonable expectation of success since such a technique is routinely practiced in liposomal art as evident from Hauser.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that the object of the present invention is to provide liposomes containing triterpenoid at a high concentration while using non-toxic solvent without intensive mechanical treatment and In order to incorporate triterpenoid at a high concentration uniformly into a liposome, the present invention employs triterpenoid having acid group, and by adding a base, the triterpenoid is transformed Into its salt having surface activity. The transformed triterpenoid salt is a surfactant of high HLB, and it forms a mixed micelle system when mixed with low HLB lipid. According to applicant, by adding an acid to decrease its pH to 5-8, the triterpenoids salt transforms back to the original form having an acid group, and thereby loses its surface activity and results in changing the mixed micelle system into a liposome. Applicant argues that Touitou merely disclose(s) the use of TEA in the example of a gel preparation, but it does not disclose the reason why TEA is added to the gel preparation. Applicant further

argues that Touitou does not disclose the combined use of base and triterpenoid to convert the acid moiety into its salt having surface activity as to form mixed micelle system with low HLB lipid. This argument is not persuasive since the percentage of drugs encapsulated in Touitou is 3 % as evident from the examples. Instant claims recite a range of 0.0001 to 5% of the drug and it is unclear as to how this can be considered as high encapsulation. With regard to applicant's arguments that the use of surfactant is not required, the examiner points out that instant claim language does not exclude a surfactant. Furthermore, phospholipids are surfactants.

3. Claims 19-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Touitou (5,716,638) by itself or in combination with Cauwenbergh (5,476,853), Hauser (4,619, 794) (individually or in combination) as set forth above, in further combination with Delrieu (5,962,015).

The teachings of Touitou and Cauwenbergh have been discussed above.

Delrieu while disclosing stabilized liposome formulations teaches that compounds such as triethanolamine, a common cosmetic buffer, can be added to phospholipid starting materials during the preparation of the liposomes to prevent aggregation and provide some stability (abstract, col. 2, lines 2-5). Therefore, one of ordinary skill in the art to add TEA after instant step A with a reasonable expectation of success since Delrieu teaches that TEA can be added at any state of liposome preparation.

Applicant's arguments regarding high encapsulation and the lack of need for a surfactant in instant invention have already been addressed by the examiner.

4. Claims 19-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Touitou (5,716,638) by itself or in combination with Cauwenbergh (5,476,853), Hauser (4,619, 794) (individually or in combination) or these references in further combination with Delrieu (5,962,015) as set forth above, further in view of WO 01/17523 of record or vice versa: that is, WO 01/17523 in view of Touitou by itself or in combination with either Cauwenbergh, Hauser or Delrieu.

WO teaches liposomal skin compositions containing triterpenoids, ursolic acid (page 1, lines 20-31). The method of preparation involves dissolving ursolic acid, phosphatidylcholine in ethanol and then adding this mixture to water (Example 1). WO however, does not teach the inclusion of propylene glycol or prepare the liposomes by the addition of TEA.

The use of ursolic acid as the terpene in the generic teachings of Touitou or in the teachings of Touitou, Cauwenbergh and Delrieu with a reasonable expectation of success since WO teaches that ursolic acid can be encapsulated in liposomes for skin treatment. Alternately, the use of the method of Touitou in WO would have been obvious to one of ordinary skill in the art since according to Touitou the ethasomes prepared by the method taught are softer and have enhanced skin permeability for various compounds (col. 2, lines 3-24).

5. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Touitou (5,716,638) by itself or in combination with Cauwenbergh (5,476,853), Hauser (4,619, 794) (individually or in combination) or these references in further combination with Delrieu (5,962,015) as set forth above, further in view of WO 01/17523 of record or vice versa: that is, WO 01/17523 in view of Touitou by itself or in combination with either Cauwenbergh, Hauser or Delrieu further in view of Hayashi (US 4,606,911).

The teachings of Touitou, Cauwenbergh, Hauser, Delrieu and WO have been discussed above. What is lacking in these references is the use of liposomal triterpenoids in tooth paste.

Hayashi teaches that triterpenoids are useful in the prevention of dental carries and suggests compositions in the form of tooth-paste (Examples and claims).

The use of the terpenoids in the form of tooth-pastes in the teachings of Touitou, Hauser, Cauwenbergh, Delrieu and WO would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Hayashi teaches the effectiveness of terpenoids in the prevention of dental carries.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore /
Primary Examiner, Art Unit 1612

GSK